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SERO-NEGATIVE MATERNAL SYPHILIS*†

REPORT OF A CASE

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Until recent years the serological investigation of possible treponemal disease was limited to the demonstration of reagin in the patient's serum, but since the introduction of the treponemal immobilization test (TPI) and the fluorescent treponemal antibody (FTA) test the physician has been able to assess with much greater confidence the significance of positive or equivocal results to standard serum tests for syphilis (STS) initially reported at routine screening.

The screening tests themselves have been so far refined that a positive report on two tests for reagin—one of them preferably highly sensitive, with a positive Reiter protein complement-fixation (RPCF) test, indicates with a very high degree of probability that the patient has, or has had, a treponemal infection (Sequeira, 1962).

Nonetheless a definite diagnosis of treponemal disease would not now be considered justified, in the absence of signs or history, without the confirmation of a positive TPI or FTA test. However, where sections of the normal population are subjected to routine screening tests for syphilis (for example blood donors and antenatal patients), these confirmatory treponemal tests will be employed only when the initial screening tests have been reported positive or equivocal—unless clinical signs, history, or some other factors arousing suspicion indicate the necessity for further investigation.

Thus the very rare false negative results given on initial screening are likely to escape detection and can be investigated retrospectively only when some subsequent event or finding arouses suspicion.

The birth of a congenital syphilitic infant to an apparently healthy sero-negative mother, though a comparatively rare event, was well documented in the older literature (Stokes, Beerman, and Ingraham, 1944). The failure to find any serological evidence during pregnancy in such cases is not surprising when one considers the relative crudity and lack of standardization of techniques in the reagin tests in use at the time.

Such an event in this era is an important reminder of the fallibility of all tests and of the unpredictability of syphilis. But it must now be extremely rare for a pregnant woman, with syphilis of sufficient duration for the elaboration of antibodies, to slip through the antenatal serological "screening net", especially when that net consists of the performance of three separate tests on all antenatal sera and the combination of tests is aimed at the detection of at least two different antibodies, and when the laboratory performing the tests has high standards of technique and an abundant experience.

The young mother of a congenitally syphilitic infant is much more likely to have by-passed the antenatal screening tests altogether, by acquiring the disease after the antenatal screening has been performed, or by failing to attend for antenatal care, or by attending too late in pregnancy, or by the omission of such tests from her antenatal investigations. On the other hand an older mother, whose syphilis is of long duration and whose circulating antibodies are not present at the time of antenatal examination in concentrations detectable by a selected group of modern screening tests, is more likely than not to produce a non-syphilitic child.

It is thus extremely rare, if not unique, to find in the literature a reasonably comprehensive serological history of a mother who was repeatedly sero-negative on routine antenatal tests but who gave birth to a child thought to be a true congenital syphilitic, and in whom subsequent serological studies revealed previously undetected specific antibodies.

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Case Report

A Negress migrated with her husband from British Guiana to the United Kingdom in 1958 when she was 38 years old.

In 1964 the husband, then aged 45 years, was found to have an aneurysmal enlargement of the innominate artery and a positive blood Wassermann reaction (WR). Tests of the cerebrospinal fluid gave the following results:

Cells: 250 per ml. (100 per cent. lymphocytes).
Lange: 5555530000.
Globulin: increased.
Cardiolipin WR, Price's precipitation reaction, and RPCF test: all positive.

There were no abnormal neurological signs and his mentality and memory were unimpaired. He was treated and has made satisfactory progress.

The wife was also seen at this time; there was no history of treponemal infection, there were no clinical signs of syphilis, and her serum test results were reported as follows:

Cardiolipin Wasserman reaction: negative.
Price's precipitation reaction: negative.
Reiter protein complement-fixation test: negative.

She had four children, all born in the United Kingdom, and there was no history of pregnancy or miscarriage before her migration. She had never had penicillin before migrating and this drug had been prescribed only twice during her stay in the United Kingdom (February, 1964, oral penicillin 250 mg. three times a day for 4 days, and an exactly similar course in October, 1965). Her antenatal records showed that in all four pregnancies she had been sero-negative at the time of testing. In the first two pregnancies only the WR and Kahn test had been performed, but in the third and fourth pregnancies the routine antenatal serum tests consisted of the CWR, PPR, and RPCF test. All four children were stated to be very well, including her infant daughter then aged 10 months. In view of the mother's serological history and her complete absence of signs it was not considered necessary to see the children at this time.

In November, 1965, the youngest child, born in July, 1963, was admitted to the Royal Hospital for Sick Children, Bristol. She had progressed very satisfactorily since birth until about 6 months before admission when her appetite began to fail and she started to lose weight (on admission 18 lb. 4 oz./8·3 kg.). For the previous 2 months there had been attacks of vomiting each evening and there was also a tendency to Pica in that she would eat dirt, coke, grass, and leaves, etc., but refuse normal food. Investigations showed her to have a marked hypochromic anaemia and positive serum tests for syphilis.

Hb: 5·7 g. per cent. The film showed marked hypochromia.
Histamine test meal: Virtually no free acid produced in response to histamine.
Sickling test: negative.
Serum iron: 25 μg./100 ml.
P.B.I.: 6·5 μg./100 ml.
Stool: No parasites or pathogens; occult blood negative.
Serum protein: 7 g. per cent., albumin 2·5, α_1 globulin 0·4, α_2 globulin 1·1, β globulin 1·2, γ globulin 1·8. g. per cent.
Alkaline phosphatase: 18 K.A. units.
Serum bilirubin: 0·2 mg. per cent.
Blood urea: 21 mg. per cent.
Calcium: 8·6 mg. per cent.
Plasma inorganic phosphate: 4·6 mg. per cent.
Hb electrophoresis: Hb A+ normal A2.

There were no positive physical signs of syphilis in the child but serum tests gave the following results:

Cardiolipin WR	positive	Bristol Laboratory
Price's precipitation reaction	negative	Bristol Laboratory
Reiter protein complement fixation test:	positive	Bristol Laboratory
Cardiolipin WR:	positive	V.D. Reference Laboratory, London
VDRL slide test:	positive 1 in 2	V.D. Reference Laboratory, London
Reiter protein complement-fixation test:	positive	V.D. Reference Laboratory, London
Treponemal immobilization test:	positive	V.D. Reference Laboratory, London
Fluorescent treponemal antibody test:	positive	V.D. Reference Laboratory, London

These tests were repeated and confirmed by both laboratories. Tests of the CSF and *x* rays of the skull and long bones showed no abnormality.

The child was then treated for congenital syphilis and has since made very satisfactory progress.

The mother was seen again at this time with her three elder children (November, 1965). The three children proved to be well cared for, healthy, and free from signs of syphilis. They were completely sero-negative (CWR, PPR, TPI, RPCF, and FTA tests). Again the mother showed no clinical sign of syphilis and the three tests were all negative. The V.D. Reference Laboratory, London, also reported on this sample of the mother's serum as follows:

Cardiolipin WR: negative.
VDRL slide test: negative.
Reiter protein complement-fixation test: weakly positive.
Treponemal immobilization test: negative.
Fluorescent treponemal antibody test: negative.

The weakly-positive RPCF test could not be regarded as evidence of a treponemal infection in the presence of negative TPI and FTA tests but, in view of this finding, the mother's serum was re-examined a month later. On this occasion both laboratories reported the serum negative to all tests including the RPCF, TPI, and FTA tests, although Dr A. E. Wilkinson, commenting on this report from the V.D. Reference Laboratory, London, observed that "on using the absorbed FTA test, I was able to detect a low titre of anti-treponemal antibody".

Unfortunately it proved impossible to persuade the patient to attend again until a year later (January 9, 1967). On this occasion the two laboratories reported

on her serum as follows:

Cardiolipin WR:	negative	Bristol Laboratory
Price's precipitation reaction:	negative	Bristol Laboratory
Reiter protein complement-fixation test:	negative	Bristol Laboratory
Cardiolipin WR:	negative	
VDRL slide test:	negative	
Reiter protein complement-fixation test:	positive	V.D. Reference Laboratory, London
Treponemal immobilization test:	positive	V.D. Reference Laboratory, London
Fluorescent treponemal antibody test:	positive	V.D. Reference Laboratory, London

Thus for the first time, some 3½ years after the birth of a syphilitic child, there appeared some serological evidence of syphilis in the mother. The serum proteins were investigated with the following results:

Total serum proteins: normal.

Serum albumin: normal.

Globulin fraction appeared to be slightly raised on electrophoresis and this appeared to be due to a slight rise in the IgG fraction as both the IgA and IgM fractions were within normal limits.

Serum protein: 7·2 g. per cent.

Electrophoresis	albumin	4·0 g. per cent.	
	α_1 globulin	3·2 g. per cent.	
	α_2 globulin		
	β globulin		
	γ globulin		

IgA 300 mg. per cent. (normal 140–420 mg. per cent.)

IgG 2,200 mg. per cent. (normal 800–1,700 mg. per cent.)

IgM 160 mg. per cent. (normal 50–190 mg. per cent.)

These results provide no possible explanation of this serological problem. A month later (February 8, 1967) the serum tests were repeated again; the FTA and RPCF tests were still positive, but the TPI test was negative, but as the serologist observed, fluctuations of this sort do occur in long standing cases of syphilis.

Thus in the later, more specific tests, some evidence of the presence of specific antibodies was detected in the mother's serum on each occasion.

The serological findings in the mother and the infected child are summarized in the Table (opposite).

This serological pattern, with the absence of signs or history of yaws and the presence of late syphilis in the husband, seemed to lead to the inescapable conclusion that the mother had latent syphilis, probably of many years' duration, which standard serum tests had failed to detect in any of her four pregnancies.

The possibility that the child might have been infected after birth was considered. Accidental infection by the father who had late cardio-vascular and asymptomatic neurosyphilis did not merit serious consideration, but the possibility that the child had been in contact with some person with early cutaneous or mucocutaneous syphilitic lesions was investigated. Several of the residents in the rather over-crowded immigrant household in which the child lived were serum tested and all proved negative. Many others had left and could not be traced, hence this possibility could not be disproved. But the incidence of early syphilis in Bristol during the relevant period was extremely low and the circle of associates of this immigrant Negro family was very restricted. Between the birth of the child in July, 1963, and diagnosis in November, 1965, only fifteen cases of early syphilis were seen among Bristol residents. Of these, fourteen were white males, nine of them homosexuals. Only one early case was seen in an immigrant during the relevant period. This was a Negress with secondary syphilis who was quite unknown to the family and as far as could be ascertained had never met the parents or children. Thus the possibility of the child's having been in contact with, and infected by, some person in Bristol with early syphilitic surface lesions must be extremely remote.

The balance of probabilities therefore seems much in favour of the conclusion that the fourth child was infected in utero by her mother who had previously produced three non-syphilitic children but who nevertheless had latent syphilis which routine serum tests had failed to detect in any of her four pregnancies.

Summary

A Negro from former British Guiana and his wife migrated to the United Kingdom in 1958. In 1964 the husband was diagnosed and treated for cardiovascular and asymptomatic neurosyphilis. His wife was sero-negative and had no signs of syphilis. Her antenatal serum tests had been negative in all her four pregnancies.

At the age of 2½ years her fourth child was diagnosed and treated for congenital syphilis, her three elder children being sero-negative and non-syphilitic. The mother's serum tests including the TPI and FTA tests were still negative at this time, but 3½ years after the birth of this fourth child results of tests for immobilizing antibody fluctuated between negative and positive and the FTA tests showed a low titre of anti-treponemal antibody; RPCF tests were weakly positive.

From this serological evidence and the family history it was concluded that the mother had latent syphilis of long standing which the standard antenatal serum tests for syphilis had failed to detect in any of her four pregnancies, and that this failure had resulted in the birth of a congenital syphilitic child to a sero-negative syphilitic mother.

The author is indebted to Dr Beryl Corner, Consultant Paediatrician, Bristol Royal Hospital for Sick Children, for permission to quote the findings on the child and to Dr A. E. Wilkinson of the Venereal Disease Reference Laboratory, London, for his observations on the serological problems.

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TABLE
SERO-NEGATIVE MATERNAL SYPHILIS SEROLOGY OF MOTHER AND INFECTED CHILD

Date	Mother's Serology		Infected Child's Serology		Observations
August, 1959	WR Kahn	negative negative			1st child born January, 1960 Non-syphilitic
October, 1960	WR Kahn	negative negative			2nd child born April, 1961 Non-syphilitic
January, 1962	C/WR PPR RPCF test	negative negative negative			3rd child born May, 1962 Non-syphilitic
March, 1963	C/WR PPR RPCF test	negative negative negative			4th child born July, 1963 Congenital syphilis diagnosed at age $2\frac{1}{2}$ years
May, 1964	C/WR PPR RPCF test	negative negative negative			Husband diagnosed and treated for cardiovascular and neurosyphilis
November, 1965	C/WR PPR RPCF test	negative negative negative	PPR C/WR RPCF test	negative positive positive	4th child diagnosed and treated for congenital syphilis
	*C/WR VDRL TPI FTA test RPCF test	negative negative negative negative weak positive	*C/WR VDRL RPCF test TPI FTA test	positive positive $\frac{1}{2}$ positive positive positive	Three eldest children: C/WR, PPR, and RPCF test, all negative
December, 1965	C/WR PPR RPCF test	negative negative negative			
	*C/WR VDRL RPCF test TPI FTA test	negative negative negative negative negative			
January 9, 1967	C/WR PPR RPCF test	negative negative negative			
	*C/WR VDRL RPCF test TPI FTA test	negative negative positive positive positive	*C/WR VDRL RPCF test FTA test	positive positive (neat) positive positive	Three eldest children: C/WR, PPR, RPCF test, TPI, and FTA test, all negative
February 8, 1967	*C/WR VDRL TPI RPCF test FTA test	negative negative negative positive positive			Mother treated for latent syphilis
April 20, 1967	*RPCF test FTA test VDRL C/WR TPI	weakly positive positive negative negative negative	*RPCF test VDRL C/WR FTA test TPI	positive weak positive positive positive positive	

* Results reported by V.D. Reference Laboratory, London.

Un cas de syphilis maternelle donnant une réaction séro-négative

RÉSUMÉ

Un nègre venant de la Guyane Brittanique et sa femme avaient émigré au Royaume-Uni en 1958. En 1964 une syphilis cardio-vasculaire et nerveuse avec des symptômes avait été diagnostiquée chez lui et traitée. Sa femme était séro-négative et ne montrait aucun signe de syphilis. Les analyses de son sérum pendant la période prénatale de ses quatre grossesses avaient été négatives.

A l'âge de deux ans et demi, son quatrième enfant a été diagnostiqué et le traitement pour la syphilis congénitale institué, les trois enfants plus âgés etaient séro-négatifs et non-syphilitiques. Les tests TPI et FTA du sérum de la mère étaient, à ce moment, encore négatifs, mais trois ans et demi après la naissance de ce quatrième enfant les résultats des tests pour l'immobilisation de l'anticorps avaient varié entre négatifs et positifs à un bas titrage et le test FTA avait montré un titrage de l'anticorps de l'anti-tréponème; les tests RPCF étaient faiblement positifs.

De ces données sérologiques et de l'historique de cette famille il a été conclu que la mère avait une syphilis latente de longue durée que les tests standards pour la syphilis faits avec le sérum prénatal n'avaient pas démontré pendant aucune de ses grossesses, et que ces échecs avaient permis la naissance d'un enfant atteint de syphilis congénitale d'une mère syphilitique dont le sérum donnait une réaction sero-negatif.